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Evaluation of a clinical pulmonary infection score in the diagnosis of ventilator-associated pneumonia

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ABSTRACT

The most important dilemma in the diagnosis of ventilator-associated pneumonia (VAP) based on only clinical findings is overdiagnosis. The aim of the study is to prospectively evaluate the Clinical Pulmonary Infection Score (CPIS) in relation to VAP diagnosis.

Design. Prospective, in a cohort of mechanically ventilated patients.

Setting. The intensive care unit of a university hospital.

Patients. Fifty patients, on mechanical ventilation therapy for more than 48 hours, suspected of having VAP were enrolled in the study and bacteriologic confirmation was done by bronchoalveolar lavage (BAL) culture.

Interventions. Bronchoscopy with BAL fluid culture after establishing a clinical suspicion of VAP in patients having no prior antibiotic therapy or no change in current antibiotic therapy within last three days before BAL.

CPIS scores during diagnosis were 6±2 (3-9) (median±QR, maximum-minimum) and it was 7±2 (2-9) at the 72nd hour, in 41 cases with a diagnosis of VAP. In cases with no diagnosis of VAP, the CPIS scores were found to be 6±2 (4-8) and 5±3 (2-7), respectively. There was no significant difference between the VAP group and the non-VAP group at diagnosis, but was significant at 72nd hour (respectively, p=0.551 and p=0.025).

CPIS scores during diagnosis were 6±3 (4-8) (median± QR, maximum-minimum) and 7±4 (2-8) at the 72nd hour, in 14 cases with a diagnosis of early-onset VAP. In cases with a diagnosis of late-onset VAP, the CPIS scores were found to be 6±2 (3-9) and 7±2 (3-9), respectively. There was no significant difference between the early-onset VAP group and the late-onset VAP group. In conclusion, the CPIS results should be evaluated carefully in the clinical setting during the diagnosis.

Key words: ventilator associated pneumonia, CPIS, VAP diagnosis

Introduction

Ventilator-associated pneumonia (VAP) is pneumonia which develops 48 hours after intubation in a subject supported by mechanical ventilation without documented pneumonia or findings suggestive of pneumonia during intubation. VAP is a complication of intubation and mechanical ventilation. (1,2)

VAP occurs in 9-27% of all intubated patients. (3,4) VAP is the leading cause of nosocomial mortality for patients with respiratory failure and crude mortality rates are reported between 20-70%. (5)

Clinical suspicion of pneumonia is the first step in any evaluation of patients with possible VAP. Diagnosis of VAP is quite difficult and there is no established consensus on the appropriate diagnostic strategy. Although the pre-

sence of radiologically observed infiltrates in a subject with fever, leukocytosis or purulent tracheobronchial secretion has a substantially high sensitivity for the diagnosis of VAP, its specificity is low. (6) In addition, the controversy remains about selection of the methods for obtaining lower respiratory tract secretions, such as endotracheal aspirate, bronchoalveolar lavage (BAL) or protected brush specimen.

The most important dilemma in the diagnosis of VAP, based on only clinical findings, is overdiagnosis. On the other hand, several studies have shown that immediate initiation of appropriate antibiotics was associated with reduced mortality. (7,8) Strategies have been proposed for the identification of low-risk patients who can receive short-term therapy, thereby minimizing the risk of delayed antimicrobial treatment as well as the risks associated with overtreatment. Clinicians need to make immediate treatment decisions in the presence of clinical suspicion of VAP based on classical criteria or a clinical pulmonary infection score (CPIS) during the initial evaluation of the patient.

Pugin et al. combined information on body temperature, white blood cell count (WBC), volume and appearance of tracheal secretions, oxygenation, chest X-ray, and tracheal aspirate culture into a clinical pulmonary infection score. (9) This score summarizes the major features used to diagnose pneumonia and gives them relative significance.

The aim of our study is to calculate sensitivity, specificity, positive and negative predictive values of CPIS in patients with VAP, diagnosed with quantitative BAL cultures.

Table 1. Clinical Pulmonary Infection Score (CPIS) criteria used in this study.

Component	Value	Point
Temperature ^0C		
	≥36.5 and ≤38.4	0
	≥38.5 and ≤38.9	1
	≥39.0 and ≤36.0	2
Blood leukocytes (mm3)	≥4000 and ≤11000	0
	<4000 or >11000	1
Tracheal secretions	Few	0
	Moderate	1
	Large and purulent	2
	(>25 PNL per LPF)	
Oxygenation		
(Pa02/Fi02, mm Hg)	>240 or presence of ARDS	0
	≤240 and absence of ARDS	2
Chest radiograph	No infiltrate	0
	Patchy or diffuse infiltrate	1
	Localized infiltrate	2
Progression of pulmonary		
Infiltrate	No radiographic progression	0
	Radiographic progression	2
	(After CHF and ARDS excluded)	
Culture	<10000 cfu bacteria	
	per ml BAL or no growth	0
	≥10000 cfu bacteria	
	per ml BAL	1

ARDS, Acute Respiratory Distress Syndrome; BAL, Bronchoalveolar Lavage; CFU, Colony Forming Unit; CHF, Congestive Heart Failure; CPIS, Clinical Pulmonary Infection Score; $Fi0_2$, Fraction of inspired oxygen; LPF, Low Power Field; $Pa0_2$, Partial arterial oxygen; PNL, Polymorphonuclear Neutrophils.

Materials and methods

A total of 50 patients, older than 18 years of age, with clinically suspected VAP and having no prior antibiotic therapy or no change in current antibiotic therapy within the last three days before BAL, were enrolled in the study. These patients received mechanical ventilation therapy for more than 48 hours and were followed up in the Reanimation ICU (surgical-medical intensive care unit). The study was approved by Uludağ Univ. School of Medicine's Ethics Committee. Signed informed consent was obtained from all patients. Clinical suspicion criteria for VAP were defined as the presence of new or progressive infiltration in chest radiography and presence of at least two of the following criteria: fever (≥38^0C), leukocytosis (≥10000 per mm^3) and purulent tracheobronchial secretion. (1,10) During clinical suspicion of ventilator associated pneumonia blood cultures were obtained twice after a 30 min-interval, and the following protocol was performed, in the same sequence, in all cases within 12 hours. First, endotracheal aspiration was performed using a sterile technique. The catheter was introduced through the endotracheal tube to a depth of at least 30 cm. Gentle aspiration was performed without instilling saline solution. The first aspirate was discarded, and the second was collected for evaluation. (11)

BAL was performed by wedging the bronchoscope in the subsegmental bronchus of the most compromised lobe seen on chest radiography or, in cases of diffuse radiologic presentation, in the posterior bronchus of the lower lobe. As little topical lidocaine as possible was used so as not to interfere with bacterial growth (never >20 mg per bronchus). Aspiration of secretions through the bronchoscope was avoided. Three aliquots were separately

Table 2. Demographic and clinical characteristics of 50 patients enrolled in the study.

	Patients with VAP (n=41) Median±QR (Max-Min)	Patients without VAP (n=9) Median±QR (Max-Min)
Age	52±39(19-85)	56±34(25-64)
Sex (Female/Male)	12/29	5/4
GCS	9±9(3-15)	11±9(6-15)
ALI/ARDS score	1.75±0.88(1-3)	1.75±1.75(1-3.75)
APACHE II score**	17±11(5-42)	26±17(4-34)
MV duration (days)	19±18(5-110)	15±9(8-22)
ICU duration (days)*	30±16(10-110)	16±9(10-27)
Presence of SIRS	9/41	3/9
Cause of ICU admission		
Trauma	11	0
COPD	6	3
Intoxication	4	2
SAH	4	1
Postoperative respiratory failure	3	1
Heart failure	3	0
Meningitis	2	1
CVD	2	0
M. Gravis	2	0
Cardiac arrest	2	0
Hellp Syndrome	1	0
Tetanus	0	1
TOF	1	0

ALI/ARDS, Acute Lung Injury/Acute Respiratory Distress Syndrome; APACHE, Acute Physiology And Chronic Health Evaluation score; COPD, chronic obstructive pulmonary disease; CVD, Cerebrovascular Disease; GCS, Glasgow Coma Score; ICU, Intensive Care Unit; MV, Mechanical Ventilation; SAH, Subarachnoid Hemorrhage; SIRS, Systemic Inflammatory Reaction Syndrome; TOF, Tracheo-Oesophageal Fistula; VAP, Ventilator-associated pneumonia.

instilled and retrieved. A first aliquot of 20 ml distilled water was instilled, gently aspirated with a syringe, and stored for another analysis. Two 60 ml-aliquots of sterile saline solution were then separately instilled and aspirated, pooled, and sent for microbiologic analysis. (12)

A Gram's stain of the tracheal aspirates was prepared and examined for WBCs and microorganisms. The presence of polymorphonuclear neutrophils (PMN) was determined in Gram stain and graded per low-power field. (13)

Five ml of BAL vortexed and 10 μl and 1μl(calibrated loop method) was cultured on sheep's blood, chocolate agar, and Eosin Methylene Blue Agar (EMB) plates and all plates were incubated overnight in a 5% carbon dioxide incubator at 37^{o}C. Isolates were characterized by colony morphology and Gram stain. The results were expressed as colony-forming units per milliliter (cfu/ml) of the original 1 ml dilution. (14)

A Gram's stain and Giemsa stain of the centrifuged BAL was prepared and examined for WBCs, differential count of leukocytes and microorganisms. The presence of PMN was then determined in Gram stain and graded per low-power field. (13,14) Growth of ≥10000 cfu/ml in BAL cultures was considered significant. Quantitative assessment was based on the dominant bacteria in the culture. (15) BAL positivity was accepted as confirmation of VAP.

Pneumonia, which developed within the first 4 days of intubation, was classified as early pneumonia and pneumonia which developed day 5 or later, as late pneumonia. (16)

The following data were routinely and prospectively recorded in patient charts at pre-specified time points (at diagnosis and third day of diagnosis): fever, leukocyte count, CPIS, PaO_2/FiO_2 (Partial arterial oxygen/Fraction of inspired oxygen), character of tracheal secretions and radiological evaluations.

The CPIS calculation at baseline was assessed by using the first five variables shown in table 1, which were modified by Luna et al. (17) CPIS at 72 hr was calculated based on all seven variables and took into consideration the progression of the infiltrate and culture results of the BAL. Pathogenic bacteria grown at significant concentrations (BAL $\geq 10^4$ CFU/ml) were allocated 1 point and cultured non-significant concentrations or no growth received 0 points.

Antibiotic therapy was prescribed by the responsible attending infectious diseases physician.

Statistical analysis

Data are expressed as median±interquartile range (QR), minimum-maximum. Fischer and Pearson Chi-square tests, Mann-Whitney U test and Receiver Operating Characteristics (ROC) curve analysis were used for statistical analysis of data. $P<0.05$ was considered significant. The sensitivity, specificity and positive and negative predictive values (PPV, NPV) of CPIS were determined by comparing patients with VAP and non-VAP.

Results

Fifty patients suspected of having VAP were enrolled in the study. Demographic and clinical characteristics of the 34 male and 16 female patients are shown in table 2. The final diagnosis of VAP was confirmed by results of BAL in 41 (82%) of the 50 patients, suspected of having clinical VAP. Antibiotics were being used in 22 of the 50 patients during BAL. Twenty of these 22 patients were in the VAP group. The Acute Physiology And Chronic Health Evaluation II (APACHE-II) score was 17±11 (5-42) in the VAP group, whereas it was 26±17 (4-34) in the non-VAP group; the difference was found to be significant ($p<0.05$). Of 41 patients whose diagno-

Table 3. Demographic and clinical characteristics of 41 patients with early-onset and late-onset VAP.

	Patients with early-onset VAP (n=14) Median±QR (Max-Min)	Patients with late-onset VAP (n=27) Median±QR (Max-Min)
Age	46±29(19-83)	52.5±43(19-85)
Sex(Female/Male)	4/10	8/19
ALI/ARDS score	2±0.75(1.25-2.50)	1.62±0.75(1-3)
APACHE II score	17±11(11-29)	17.5±11(5-42)
MV duration (days)*	16±10(5-46)	22.5±23(10-110)
ICU duration (days)	30±23(10-65)	31.5±16(10-110)
GCS	9±9(4-15)	9±9(3-15)
Presence of SIRS	3/14	6/27
Microorganisms		
A.baumannii	4	8
P.aeruginosa	5	6
MRSA	0	7
MSSA	2	0
E.coli	0	1
K.pneumoniae	1	1
P.mirabilis	1	0
S.pneumoniae	1	0
P.putida	0	1
A.lwoffii	0	1
S.maltophilia	0	1
E.cloacae	0	1

ALI/ARDS, Acute Lung Injury/Acute Respiratory Distress Syndrome; APACHE, Acute Physiology And Chronic Health Evaluation score; GCS, Glasgow Coma Score; ICU, Intensive Care Unit; MRSA, Methicillin-Resistant Staphylococcus aureus; MSSA, Methicillin-Sensitive Staphylococcus aureus; MV, Mechanical Ventilation; SIRS, Systemic Inflammatory Reaction Syndrome; VAP, ventilator associated pneumonia .

Table 4. Sensitivity, specificity, positive and negative predictive values of CPIS in 50 patients with diagnosis of VAP and non-VAP at the time of diagnosis and at the 72nd hour.

Threshold value	CPIS>7	CPIS>6	CPIS≥6	CPIS≥5
Sensitivity-D(%)	80	76	80.7	80
Specificity-D(%)	17	15	16.6	10
PPV-D(%)	10	31	51	78
NPV-D (%)	89	55	44	11
Sensitivity-L(%)	100	87 (83)	88 (85)	86
Specificity-L(%)	23	22 (17)	33 (20)	37
PPV-L (%)	31	55 (26)	78 (47)	86
NPV-L(%)	100	62 (75)	50 (62)	37

CPIS, Clinical Pulmonary Infection Score; D, At the diagnosis; L, At the 72nd hour; NPV, Negative predictive value; PPV, Positive predictive value; VAP, ventilator associated pneumonia.
* Calculated values using first 5 variables

ses were confirmed by BAL, fourteen (34%) had early-onset pneumonia and 27 (66%) had late-onset pneumonia (table 3).

CPIS which were calculated during diagnosis and at the 72nd hour were evaluated in relation to VAP diagnosis on the basis of 41 patients whose diagnoses were confirmed by BAL. Sensitivity, specificity, positive and negative predictive values of CPIS at diagnosis and at the 72nd hour are shown in table 4.

Comparison of the CPIS values (on the basis of five parameters), confirmed by BAL for the 41 patients, during diagnosis and at the 72nd hour demonstrated that CPIS values at the 72nd hour increased in 11 cases, did not change in 10 cases, and decreased in 17 cases (three cases were not evaluated due to death). For the remaining nine patients, whose diagnoses were not confirmed by BAL, evaluation demonstrated that CPIS scores increased in two cases, decreased in five cases and did not change in one case (one case was not evaluated due to death).

In 41 cases with a diagnosis of VAP, CPIS scores during diagnosis were 6±2 (3-9) (median± QR, maximum-minimum) and 7±2 (2-9) at the 72nd hour,. In cases with no diagnosis of VAP, the CPIS scores were found to be 6±2 (4-8) and 5±3 (2-7), respectively. There was no significant difference between the VAP group and the non-VAP group.

The differences (delta) between the initial versus 72nd h CPIS scores were not statistically significant when comparison was made between VAP and non-VAP patients.

In 14 cases with a diagnosis of early-onset VAP, CPIS scores during diagnosis were 6±3(4-8) (median± QR, maximum-minimum) and 7±4(2-8) at the 72nd hour. In cases with a diagnosis of late-onset VAP, the CPIS scores were found to be 6±2 (3-9) and 7±2 (3-9), respectively. There was no significant difference between the early-onset VAP group and the late-onset VAP group. The differences (delta) between the initial versus 72nd h CPIS scores were not statistically significant when comparison was made between early-onset and late-onset VAP.

There was no significant correlation between APACHE II score and CPIS at 24th and 72nd hour.

Discussion

The diagnosis of VAP is still controversial. In some studies it was demonstrated that quantitative evaluation of lower

respiratory tract sample obtained by bronchoscopy was more sensitive and specific than quantitative evaluation of endotracheal aspirates. However, there are some studies where both two methods were not different from each other. In addition, the effect of invasive procedures on prognosis is still controversial. (18,19) CPIS was first defined by Pugin et al. and they demonstrated that it had a high sensitivity and specificity in the diagnosis (sensitivity 93% and specificity 100%). In this study all bacterial species, which grew in BAL fluid were evaluated quantitatively and logarithmic values were calculated. (9) This calculation, known as the bacterial index, is not accepted as a standard reference method and thus leads to controversial study results.

In this study, when the CPIS score, calculated from 5 parameters at diagnosis, was analyzed by different threshold values, it was demonstrated that sensitivity varied between 76 and 80.7% and specificity varied between 10 and 17%. On the other hand, evaluation of the CPIS score from 7 parameters for the 72^{nd} hour demonstrated that sensitivity varied between 86 and 100% and specificity varied between 17 and 37%. Analysis of CPIS scores during diagnosis or at the 72^{nd} hour demonstrated that specificity remained considerably low and that PPV increased as the threshold value decreased while it decreased as the threshold value increased.

Croce et al. evaluated CPIS with respect to the diagnosis of pneumonia, during the diagnosis. This study demonstrated the sensitivity as 61% and specificity as 43%, by use of five parameters and a CPIS threshold value of >6. (20) In this study the PPV was reported as 44% and NPV as 62%. Fartoukh et al. also used the same criteria and reported sensitivity as 60%, specificity as 59%, PPV as 60%, and NPV as 59%. (21) In this study sensitivity was 76%, specificity was 15%, PPV was 31%, and NPV was 55%, under the same conditions. Comparison of the two studies above highlights a higher sensitivity but lower specificity in our study.

In studies where CPIS was evaluated for pneumonia diagnosis at 72^{nd} hour of diagnosis, Schurink et al. found sensitivity as 83% and specificity as 17%, using 6 parameters (Modified Pugin Criteria) and the threshold value was >5 for the evaluation of CPIS. (22) In this study, the best threshold value was found to be >7 by ROC analysis and according to this threshold value sensitivity of CPIS was found to be 41%, specificity was 77%, PPV was 80% and NPV was 36% for the diagnosis of pneumonia.

In the study of Luyt et al. it was reported that sensitivity was 89%, specificity was 47%, PPV was 57% and NPV was 84% when the CPIS was evaluated using 7 parameters and CPIS threshold value was >6. (23) In addition, in this study the best CPIS threshold value was found to be >7 by ROC analysis and on the basis of this value sensitivity was found to be 75% and specificity was 66%. On the other hand, in this study we found the sensitivity as 87%, specificity as 22%, PPV as 55% and NPV as 62% for CPIS, evaluated using 7 parameters and a threshold value of >6. A CPIS reference of >7, showed that sensitivity was 100%, specificity was 23%, PPV was 31%, and NPV was 100%. Comparison of our study with the study of Luyt et al·, (23) where the same number of parameters were used demonstrated that sensitivity and PPV were similar, whereas specificity and NPV were lower.

In other studies it was reported that sensitivity varied between 30 and 77%, while specificity varied between 42 and 85%, when CPIS threshold value was >6. (24-26)

Evaluation of the results of our study and other studies demonstrated that sensitivity and specificity ratios did not attain the desired clinical levels. On the other hand it is impossible to make a precise comparison of these studies. Factors that play a role in this study could be explained by the number of parameters and the differences in obtaining microbiological samples, which were used for the calculation of CPIS, differences in pneumonia ratios of the study groups, differences in number of patients who used antibiotics during the diagnosis, difference of the method that was used as a golden standard for the diagnosis of pneumonia in the studies and heterogeneous patient populations of the study groups. (20-26)

Studies conducted on traumatized and burned patients clearly demonstrated that the effects of differences in the patient groups on results. (20-24)

Two limitations of our study should be noted. Firstly, the size of the subgroup of patients without VAP and that could have altered the results. Secondly, our patients without VAP (control group) had higher APACHE II scores.

As a consequence, results of CPIS studies and our study do not supersede conventional clinical criteria, which were first defined by Johanson et al. (27) We believe that, results of CPIS should be evaluated carefully in the clinical setting.

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